The Egyptian Journal of Medical Human Genetics (2010) **11**, 181–185

Ain Shams University

The Egyptian Journal of Medical Human Genetics

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CASE REPORT

Ellis–van Creveld syndrome with facial dysmorphic features in an Egyptian child

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Received 3 February 2010; accepted 30 May 2010

KEYWORDS

Ellis–van Creveld syndrome;
Chondroectodermal dysplasia;
Polydactyly;
Cardiovascular malformations

Abstract Ellis–van Creveld syndrome (EVC) is a chondroectodermal dysplasia. The tetrad of cardinal features includes disproportionate dwarfism, bilateral postaxial polydactyl of hands, hidrotic ectodermal dysplasia, and congenital cardiac malformations. This rare condition is inherited as an autosomal recessive trait with variable expression. Mutations of the *EVC1* and *EVC2* genes, located in a head to head configuration on chromosome 4p16, have been identified as causative. We report a patient with the typical features of the syndrome but with facial dysmorphic features (upward slant of eyes, megalocornea and high forehead), for the first time in the literature.

1. Introduction

Ellis–van Creveld syndrome (EvC syndrome, OMIM #225500), also known as chondroectodermal dysplasia, or mesoectodermal dysplasia is an autosomal recessive skeletal dysplasia that results in short-limbed disproportionate dwarfism. The disorder was first described in 1940 by Ellis and van Creveld [1]. The term chondroectodermal is used to describe the types of tissues involved in the disorder, mainly the involvement of long bones of the skeleton, nails and teeth. The term mesoectodermal dysplasia was once proposed to include the 60% incidence of congenital heart disease that occurs in association with the disorder [2,3]. The incidence being approximately in 1/5000 live births [4–6]. Other features include oral manifestations (multiple oral frenula, neonatal teeth, delayed teeth eruption, and hypodontia). Several inconstant additional clinical findings are described, including strabismus, epi- and hypospadias, cryptorchidism [3], and thoracic wall and pulmonary malformations [7]. Renal abnormalities are found in very rare cases with agenesis, dysplasia, megaureter and nephrocalcinosis. Lethal nephronophthisis has been reported only once, in a patient with short limbs, short ribs, abnormal teeth and polydactyly (considered as EvC) [8], but this diagnosis may be discussed. Hematologic abnormalities have also been rarely reported: one case with

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Peer review under responsibility of Ain Shams University.
doi:10.1016/j.ejmhg.2010.05.001

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dyserythropoiesis [9] and another associated with perinatal myeloblastic leukemia [10]. Head circumference and mental development in EvC are normal.

Family-based genetic studies identified human mutations in two genes, *EVC* and *LBN* (*EVC2*), which are located head-to-head on chromosome 4p16.2 [11–13]. Disruption of either of these non-homologous genes results in an indistinguishable heart–hand phenotype, but the role of *EVC* and *LBN* in development and disease pathogenesis remains largely unknown.

However, EvC syndrome is considered part of an emerging class of diseases called ciliopathies. The underlying cause may be a dysfunctional molecular mechanism in the primary cilia structures of the cell, organelles which are present in many cellular types throughout the human body. The cilia defects adversely affect "numerous critical developmental signaling pathways" essential to cellular development and thus offer a plausible hypothesis for the often multi-symptom nature of a large set of syndromes and diseases. Known ciliopathies include primary ciliary dyskinesia, Bardet–Biedl syndrome, polycystic kidney and liver disease, nephronophthisis, Alstrom syndrome, Meckel–Gruber syndrome and some forms of retinal degeneration [14].

We present here a clinical analysis of a male child manifesting many of the specific features of EvC, but with facial dysmorphic features for the first time in the literature.

2. Case report

A 2.5 year old male was referred to hospital because of recurrent attacks of bronchopneumonia, and heart failure. The mother suffered oligohydrominas during pregnancy and the child was delivered prematurely. He is the product of consanguineous second cousin parents, a 44 year old healthy father and 37 year old healthy mother. The mother had had two spontaneous abortions, but no information was available on the phenotype of these abortuses. There was no history of duplicate digits in either parent.

On physical examination, the patient had disproportionate short stature (his height, and weight were below the 3rd centile). The limbs were short (acromesomelic) with three limbs postaxial polydactyly in both hands (Fig. 1) and left foot. Other striking features included shortening of middle and distal phalanges, left cutaneous syndactyly between 4th and 5th toes, wide space between hallux and the rest of the toes, and short 2nd and 4th toes on left foot (Fig. 2). There were bilateral simian crease in both hands and medial deviation of right foot with overlap of the fourth toe over the third toe. His nails

Figure 2 Left postaxial polysyndactyly.

were dystrophic, friable, markedly hypoplastic, and thin. The remaining physical examination revealed a high forehead, sparse thin hair; particularly on eyebrows, hypertelorism, large low set ears, megalocornea, upward slant of palperal fissures, broad depressed nasal bridge, short bulbus nose, thin upper lip and long philtrum (Fig. 3). Oral examination revealed two upper neonatal teeth, delayed teeth eruption, fusion of the upper lip to the maxillary gingival margin and absence of mucobuccal fold, and multiple small alveolar notches on the crest of the thin alveolar ridge giving a serrated appearance, with absence of teeth (Fig. 4). Pectus carinatum with short sternum, narrow long thorax compared to the height of lower limbs, and umbilical hernia, were also detected in our patient (Fig. 5). Intelligence was in the normal range. His skeletal survey revealed radiological findings of chondroectodermal dysplasia (shortened global long bone), short metacarpals and phalanges, polydactyly, narrow chest, and cardiac enlargement. The pelvis had spiking up acetabular fossa. An echocardiogram revealed congenital heart in the form of a single atrium with mild tricuspid regurgitation and pulmonary artery hypertrophy. The findings of routine blood investigations were within normal limits. Fundus examination and MRI of the brain were normal. Karyotype was also normal.

3. Discussion

EvC syndrome is a genetic disorder with autosomal recessive transmission most often described in families with a history of consanguinity [15]. However Mostafa et al. [16] observed an unusual pattern of inheritance from father to son or to daughter in two Egyptian consanguineous families, thus demonstrating pseudodominant inheritance. In our case this has not been verified. The phenotype of our case shared many features with the description of EvC [11,17,18]. The features in

Figure 1 Bilateral postaxial polydactyly with short fingers and dysplastic fingernails.

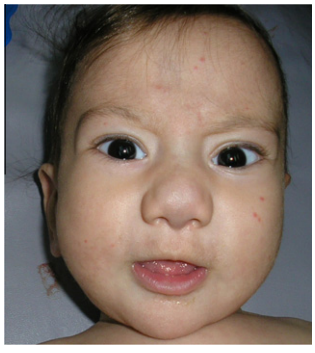

Figure 3 Facial features of the patient.

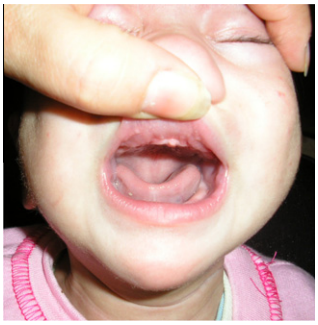

Figure 4 Anterior view of the mouth of EVC patient showing two upper neonatal teeth, absence of mucobuccal folds and normal tongue.

Figure 5 Long narrow chest and shortness of the limbs.

common with EvC include disproportionate short stature, delayed teeth eruption, and postaxial polydactyly of the hands and feet. The patient reported here manifested mesomelic and acromelic shortening of limbs that is typical for EvC. In our patient there was polydactyly in both hands and left foot. Polydactyly of the feet is present in only 10% of the patients [19].

Oral manifestations of the syndrome include the fusion of the upper lip to the maxillary gingival margin, absence of mucobuccal fold or the sulcus anteriorly, notching of the alveolar ridge, congenitally missing teeth in the mandibular anterior region, erupted teeth having small crowns and irregular spaces between teeth [20]. The absence of mucobuccal fold, which is the most striking and consistent oral manifestation of the disease was present. Neonatal teeth were also reported in our patient. Also he presented with the features of congenitally missing teeth in the mandibular anterior region, notching of the alveolar ridge, and fusion of the upper lip to the maxillary gingival margin. Mostafa et al. [16] reported a new consistent orodental anomaly (bifid tip of the tongue) in six Egyptian cases of EvC syndrome. However, this anomaly was not reported in our patient.

In our case there was short stature due to shortness of lower legs. Mitchell et al. reported that shortness in EvC is present at birth and becomes more apparent with subsequent growth [21,22]. Baujat and Le Merrer have demonstrated that growth hormone treatment of these patients is not effective [23]. However, it is important to highlight that there is one case published in the literature in which a favorable result in growth is described following hormonal treatment [24].

A major feature of EvC is a narrow thorax [3]. The patient reported here had narrow thorax with pectus carinatum. The nails were short, and hypoplastic as reported for EvC. None of the characteristic genital abnormalities were observed in our patient. Additional clinical findings affecting other organs (lungs, kidneys, liver, pancreas and central nervous system, genitourinary anomalies) may occasionally be observed [15,25], although these were not present in our case.

In our case cardiac evaluation revealed presence of a single atrium Congenital heart malformations occur in about 50–60% of cases and comprise of single atrium, defects of the mitral and tricuspid valves, patent ductus, ventricular septal defect, atrial septal defect and hypoplastic left heart syndrome. The presence of congenital heart disease may support the diagnosis of the EVC syndrome and appears to be the main determinant of longevity [6].

As for craniofacial morphology of this syndrome, many authors have described the face as normal [26–30]. On the other hand, there are several reports of a small cranial base, hypoplastic maxilla, mandibular proganthism and large gonial angle. Ellis–van Creveled [1] described some enlargement of the skull, depression of nasal bridge and a pointed chin. Eidelman and Rosenzweig [31] reported mandibular protrusion with an angle class III skeletal relationship and a large gonial angle. Probhu and Prabhu [32] described mandibular proganthism, and an underdevelopment of middle third of the face. The face was longer anteriorly and shorter posteriorly than normal. Thus the craniofacial morphology of this syndrome is a point of controversy. What was striking in our patient were the facial features, which were not reported previously especially upward slant, meglocornea and high forehead. Bhat, et al. [33] reported the EvC syndrome in an Indian child with facial hemiatrophy for the first time in medical literature.

It is almost impossible to radiographically differentiate Ellis–van Creveld syndrome from similar chondrodystrophies such as asphyxiating thoracic dystrophy, achondroplasias, chondroplasia punctata and Morquio's syndrome. Patients may have identical features in hands, pelvis and long bones, and differential diagnosis is made with the following clinical changes such as cardiac anomalies, nail hypoplasias, fusion of upper lip and gingiva, oligodontia and neonatal teeth, if present [34].

EvC belongs to the short rib-polydactyly group (SRP). These SRPs are all autosomal recessive disorders that have been classified into types (Saldino–Noonan syndrome, type I; Majewski syndrome, type II; Verma–Naumoff syndrome, type III; Beemer–Langer syndrome, type IV; and Jeune Dystrophy). They are characterized by hypoplastic thorax due to short ribs, short limbs, frequent polydactyly and visceral abnormalities. Radiographically and histologically, SRP III (Verma–Naumoff syndrome, OMIM 263510) mostly resembles some forms of EVC [35,36]. The question of SRP being due to mutation in the *EVC1* gene was excluded by Takamine et al. [37].

Postnatally, the essential differential diagnoses include Jeune dystrophy, McKusick–Kaufman syndrome and Weyers syndrome. Jeune dystrophy (MIM 208500) is characterized by thoracic dystrophy, shortening of the extremities and generalized bone dysplasia. Similarities and differences of patients with EvC and Jeune dystrophy have been stressed [38,39].

There are no specific constant features to confirm the diagnosis of presumptive EvC but some features, including congenital heart disease, supernumerary digits and ectodermal dysplasia will mostly support the diagnosis of EvC syndrome than Jeune dystrophy. EvC and McKusick–Kaufman syndrome (MKK, MIM 236700), both recessively inherited disorders, share post-axial polydactyly and congenital heart defect. Distinguishing characteristics are the osteochondrodysplasia and ectodermal anomalies in EvC syndrome, and hydrometrocolpos in MKK syndrome. MKK is caused by mutations in a gene on chromosome 20p12, encoding a protein similar to members of the chaperonin family. Mutation in the same gene causes Bardet–Biedl syndrome-6 [40]. Weyers acrodental dysostosis (OMIM 193530) with the same phenotype of EvC but in a milder form is the heterozygous manifestation of the *EVC* gene. Disproportionate dwarfism, heart defect and thoracic dysplasia are not present in this autosomal dominant condition [41,42].

In conclusion, Ellis–van Creveld syndrome is a rare autosomal disorder. A third of these patients die of cardiac or respiratory distress in infancy. Prenatal diagnosis in regard to intrauterine growth retardation, skeletal malformations and cardiac defects can be depicted on ultrasound images. Diagnosis is also positive using chorionic villi or amniotic fluid using linked-microsatellite markers if a previously affected sibling has been identified. A multidisciplinary approach is advocated involving a clinical geneticist, cardiologist, pulmonologist, orthopedician, urologist, physical and occupational therapist, dentist, psychologist, developmental pediatrician and pediatric neurologist for proper management and rehabilitation of such cases.

The authors declare that there is no conflict of interest. Informed consent was obtained from the parents of the child.

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